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Familial lobular breast cancer: Is testing for germline *CDH1* mutations necessary?

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Germline CDH1 mutations

Germline mutations in the E-cadherin gene (*CDH1*) confer a high lifetime risk of developing hereditary diffuse gastric cancer (HDGC) syndrome [1]. Classically, lobular breast cancer (LBC) has been described as a secondary "component" of this syndrome [2]. However, recent studies have demonstrated that LBC is associated with germline *CDH1* mutations also in the absence of a family history of gastric cancer (GC). Some of these germline mutations have been identified for the first time in LBC cases, others were previously reported in individuals diagnosed with GC [3,4].

Lobular breast cancer

In a recent review, we reported that genetic testing of individuals with a family history of LBC, found that approximately 3% of these patients carried pathogenic germline *CDH1* mutations but no mutations in the *BRCA1/2* genes [5].

A total of 482 LBC patients were genetically tested in search for constitutional *CDH1* mutations and 16 (3.2%) novel germline *CDH1* variants were identified. Bilateral LBC was diagnosed in 9.5% of cases (6/63) and 40.3% of patients (163/404) were found to have a positive family history of BC. In germline *CDH1* mutation carriers, the mean age at onset was 45 years. The type and frequency of the identified *CDH1* variants were as follows: six missense mutations (37.5%), three splice sites (18.7%), three deletions (18.7%), two insertions (13%), one non-sense (6.2%) and one stop codon (6.2%). Of the missense alterations, three were classified as "benign" and three as variants of uncertain significance (VUS).

When compared, the *CDH1* variants associated with the HDGC syndrome map to different domains of the gene, spanning almost all of its 6 exons [6].

Topics of discussion

At present, four are the main subjects of debate:

(a) Is LBC the first manifestation of the HDGC syndrome?
(b) Are germline *CDH1* alterations and *BRCA* mutations mutually exclusive?
(c) How reliable is the information that patients provide on their family history of GC?
(d) In what cases should prophylactic mastectomy be considered a viable option?

Currently, addressing the first point in a satisfactory way is not yet possible. Indeed, while women are routinely checked for breast tumor (i.e. mammography), gastric screening is normally carried out only in selected cases, as gastric tumor is hard to detect in its early stages. Since *CDH1* mutant carriers have a higher risk of developing HDGC, those found to have a breast tumor with lobular histotype should undergo gastroscopy and have their gastric mucosa monitored. In the case of *CDH1* mutation carriers, the cumulative risk of developing HDGC before the age of 80 is 70% for men (95% CI 59%–80%) and 56% for women (95% CI 44%–69%). Moreover, for women with a *CDH1* mutation, the cumulative risk of LBC before the age of 80 is around 42% (95% CI 23%–68%) [7], even in the absence of symptoms.

As for the second topic of debate, the identification of LBC patients carrying mutations in *CDH1* but not in *BRCA1/2* confirms the existence of a sub-population that is distinct from the one with *BRCA* inherited cancer predisposition, the latter being the most common hereditary breast and ovarian cancer (HBOC) syndrome [8]. Although the mutation frequency of *CDH1* is significantly lower than that of *BRCA1/2*, genetic testing for germline *CDH1* mutations is not indicated for HBOC patients with pathogenic *BRCA1/2* variations but could be recommended for those without.

As for the third point of debate, data on the patient's family history of gastric tumor may be incorrect due to information that has been wrongly reported, particularly by relatives, or to inaccuracies in genetic counseling. To minimize this risk, thorough genetic counseling should be offered to patients and third degree relatives also included. Unfortunately, it is not yet possible to estimate the risk for asymptomatic individuals with a confirmed *CDH1* mutation and familial LBC, of developing LBC. The reported frequency of *CDH1* mutations and the percentage of affected individuals are currently too low to make any meaningful assessment of cancer risk.

With regard to the fourth subject for discussion, while prophylactic total gastrectomy is seen in clinical practice as the best way to prevent HDGC in *CDH1* mutant carriers, prophylactic mastectomy is not yet considered as life-saving in this sub-population. This is due to the small number of *CDH1* mutations identified in LBC patients to date, and to the inability to reliably predict the risk of LBC in these patients. The use of ultrasound and MRI in addition to

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mammography does increase the sensitivity in detecting LBC and provides useful information for further management and presurgical planning. However, for asymptomatic and resolute women with a significant family history of BC, prophylactic bilateral mastectomy may become a viable option to consider once a pathological *CDH1* mutation has been identified. Crucially, the risk that these individuals might develop gastric cancer should never be underestimated, even in the absence of a family history of gastric tumor.

Conclusions

Our understanding of the so-called HDGC syndrome is currently incomplete. We speculate that there are carriers of germline *CDH1* mutations who present some "minor" clinical manifestations, in the absence of HDGC. It has been clearly shown that some germline *CDH1* mutations can first manifest themselves as cancers other than GC [9]. Therefore, minor phenotypes different from those typically associated with the HDGC syndrome should be taken into careful consideration.

Using the abovementioned *CDH1* genetic results as reference, we reexamined the clinical characteristics of LBC patients carrying pathogenic germline *CDH1* mutations. We concluded that testing for germline *CDH1* mutations is necessary for LBC cases that meet either of the following clinical criteria: (a) Bilateral LBC, with or without family history of LBC, and (b) Monolateral LBC with onset before the age of 45 and a family history of LBC. Considering that the probability of finding at least one germline *CDH1* alteration in this subpopulation is rather low, the adoption of wider criteria would not be justified.

Disclosure of potential conflicts of interest

Nothing to declare.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Not necessary for this study.

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Conflict of interest statement

The authors declare no competing interests.

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